

## **Hypouricemic action of selected flavonoids in mice: structure-activity relationships.**

Mo SF, Zhou F, Lv YZ, Hu QH, Zhang DM, Kong LD.

**Source** : State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, P.R. China..

### **Abstract**

Hyperuricemia and gout appear to be rapidly increasing worldwide and frequently cause symptoms of metabolic syndrome. Dietary flavonoids have their potential beneficial effects on human health. In the present study, 15 flavonoids (quercetin, morin, myricetin, kaempferol, icariin, apigenin, luteolin, baicalin, silibinin, naringenin, formonoetin, genistein, puerarin, daidzin and naringin dihydrochalcone) were selected to investigate for their hypouricemic action in mice. Oral administration of quercetin, morin, myricetin, kaempferol, apigenin and puerarin at 50 and 100 mg/kg for 3 d was able to elicit hypouricemic actions in hyperuricemic mice induced by potassium oxonate. Luteolin, formonoetin and naringenin showed the significant effects only at 100 mg/kg. Quercetin, puerarin, myricetin, morin and kaempferol significantly reduced liver uric acid level in hyperuricemic animals. In addition, quercetin, morin, myricetin, kaempferol and puerarin exhibited significant inhibition on the liver xanthine oxidase (XOD) activities. It seems to be likely that these flavonoids reduce serum urate levels by mainly inhibiting XOD activity. However, the hypouricemic effect of apigenin observed seemed not to parallel with the changes in liver uric acid level and liver XOD activity, implying that apigenin might act via other mechanisms apart from inhibiting enzyme activity simply. Analysis of the chemical structure showed that a planar structure with the hydroxyl groups played a crucial role in hypouricemic activity of flavonoids. The exact mechanism of the hypouricemic action of flavonoids in vivo should be investigated in the future.

Am J Physiol Renal Physiol. 2009 Oct;297(4):F1080-91. Epub 2009 Jul 15.

## **Allopurinol, rutin, and quercetin attenuate hyperuricemia and renal dysfunction in rats induced by fructose intake: renal organic ion transporter involvement.**

Hu QH, Wang C, Li JM, Zhang DM, Kong LD.

**Source** : State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing 210093, China.

### **Abstract**

Fructose consumption has been recently related to an epidemic of metabolic syndrome, and hyperuricemia plays a pathogenic role in fructose-induced metabolic syndrome. Fructose-fed rats showed hyperuricemia and renal dysfunction with reductions of the urinary uric acid/creatinine ratio and fractional excretion of uric acid (FE(ur)), as well as other features of metabolic syndrome. Lowering serum uric acid levels with allopurinol, rutin, and quercetin increased the urinary uric acid/creatinine ratio and FE(ur) and attenuated other fructose-induced metabolic abnormalities in rats, demonstrating that hyperuricemia contributed to the deficiency of renal uric acid excretion in this model.

Furthermore, we found that fructose upregulated the expression levels of rSLC2A9v2 and renal-specific transporter (rRST), downregulated the expression levels of organic anion transporters (rOAT1 and rUAT) and organic cation transporters (rOCT1 and rOCT2), with the regulators prostaglandin E(2) (PGE(2)) elevation and nitric oxide (NO) reduction in rat kidney. Allopurinol, rutin, and quercetin reversed dysregulations of these transporters with PGE(2) reduction and NO elevation in the kidney of fructose-fed rats. These results suggested that dysregulations of renal rSLC2A9v2, rRST, rOAT1, rUAT, rOCT1, and rOCT2 contributed to fructose-induced hyperuricemia and renal dysfunction. Therefore, these renal transporters may represent novel therapeutic targets for the treatment of hyperuricemia and renal dysfunction in fructose-induced metabolic syndrome.

## **3,5,2',4'-Tetrahydroxychalcone, a new non-purine xanthine oxidase inhibitor.**

Niu Y, Zhu H, Liu J, Fan H, Sun L, Lu W, Liu X, Li L.

**Source** : Kunming Medical University, PR China.

### **Abstract**

Xanthine oxidase is a key enzyme that catalyses hypoxanthine and xanthine to uric acid and the overproduction of uric acid will lead to hyperuricemia which is an important cause of gout. In the present study, three chalcone derivatives were synthesized and evaluated for inhibitory activity against xanthine oxidase in vitro. Of the compounds, only Compound 1, 3,5,2',4'-tetrahydroxychalcone, exhibited a significant inhibitory activity on xanthine oxidase with an IC(50) value of 22.5  $\mu$ M. Lineweaver-Burk transformation of the inhibition kinetics data demonstrated that it was a competitive inhibitor of xanthine oxidase and Ki value was 17.4  $\mu$ M. In vivo, intragastric administration of Compound 1 was able to significantly reduce serum uric acid levels and inhibited hepatic xanthine oxidase activities of hyperuricemic mice in a dose-dependent manner. Acute toxicity study in mice showed that Compound 1 was very safe at a dose of up to 5 g/kg. These results suggest that Compound 1 is a novel competitive xanthine oxidase inhibitor and is worthy of further development.

## Pharmacological basis for use of *Pistacia integerrima* leaves in hyperuricemia and gout.

Ahmad NS, Farman M, Najmi MH, Mian KB, Hasan A.

**Source** : College of Medical Sciences, National University of Sciences and Technology, Rawalpindi 46000, Pakistan.  
naseemsaud@yahoo.com

### Abstract

**ETHNOPHARMACOLOGICAL SIGNIFICANCE:** *Pistacia integerrima* Stew ex. Brandis is an important component of commonly dispensed traditional dosage forms. We wished to determine whether polyphenolic constituents of this plant could be useful in oxidative stress and have potential to counter hyperuricemia.

**MATERIAL AND METHODS:** Radical scavenging activity was determined by 1,1-diphenyl-2-picrylhydrazyl (DPPH) and xanthine oxidase (XO) inhibitory activity assay in vitro. Fructose (FRS) induced hyperuricemic animal model was used to assess the serum uric acid (UA) lowering effect by plant products.

**RESULTS:** Ethyl acetate and n-BuOH fractions had the highest DPPH radical scavenging activity. Fifty percent inhibitory concentration (IC<sub>50</sub>) was 6 and 7.6 microg/ml respectively. It was less than quercetin (IC<sub>50</sub> 0.95 microg/ml) and ascorbic acid (IC<sub>50</sub> 1.76 microg/ml). Xanthine oxidase inhibitory activity was comparable between n-BuOH and EtOAc (IC<sub>50</sub> 19 and 20 microg/ml) extracts but less than quercetin (IC<sub>50</sub> 0.65 microg/ml) and allopurinol (IC<sub>50</sub> 0.10 microg/ml). The antioxidant activity as well as the inhibitory activity towards the enzyme XO by quercetin-3-O-beta-D-glucopyranoside (5), kaempferol-3-O-beta-D-glucopyranoside (6), quercetin-3-O-(6''-O-syringyl)-beta-D-glucopyranoside (7), kaempferol-3-O-(4''-O-galloyl)-alpha-L-arabinopyranoside (8), rutin (4) together with aglycons, quercetin (1), kaempferol (2) and apigenin (3) was promising to continue in vivo hypouricemic studies. Ethyl acetate extract had dose dependent UA lowering effect in hyperuricemic mice. This effect was comparable with quercetin but less than allopurinol.

**CONCLUSIONS:** These findings are encouraging to plan clinical studies in hyperuricemic patients.

J Ethnopharmacol. 2004 Jul;93(1):133-40.

## **Effects of *Biota orientalis* extract and its flavonoid constituents, quercetin and rutin on serum uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver.**

Zhu JX, Wang Y, Kong LD, Yang C, Zhang X.

**Source** : Institute of Functional Biomolecule, State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, PR China.

### **Abstract**

The hypouricemic actions of *Biota orientalis* (BO) extract and its flavonoid constituents quercetin and rutin, were in vivo examined using oxonate-induced hyperuricemic mice. Quercetin and rutin, when administered three times orally to the oxonate-induced hyperuricemic mice, were able to elicit dose-dependent hypouricemic effects. The effects of quercetin and rutin were more potent than that of *Biota orientalis* extract at the same dose of 100 mg/kg. At doses of 50 mg/kg of quercetin or above, or at doses of 100 mg/kg of rutin or above, the serum urate levels of the oxonate-pretreated mice were not different from normal mice. In addition, *Biota orientalis* extract, quercetin and rutin, when tested in vivo on mouse liver homogenates, elicited significant inhibitory actions on the xanthine dehydrogenase/xanthine oxidase (XDH/XO) activities. The effects of quercetin and rutin resulted less potent than that of allopurinol. However, intraperitoneal administration at the same scheme did not produce any observable hypouricemic effect. These hypouricemic effects are partly due to the inhibition of XDH/XO activities in mouse liver. The pharmacological profile of the flavonoids is partly different from that of allopurinol. Such hypouricemic action and inhibition of the enzyme activity of quercetin and rutin may be responsible for a part of the beneficial effects of *Biota orientalis* extract on hyperuricemia and gout. The effects of quercetin and rutin on serum urate levels in hyperuricemic mice induced by oxonate and the inhibition of enzyme activities in mouse liver are discussed in relation to their absorption and metabolism, and their potential application to treat gout and hyperuricemia.

## **Hypouricemic and antioxidant activities of *Allium cepa* Liliaceae and quercetin in normal and hyperuricemic rats.**

Haidari F, Rashidi MR, Eshraghian MR, Mahboob SA, Shahi MM, Keshavarz SA.

**Source** : School of Health and Institute of Public Health Research, Tehran University of Medical Sciences, Tehran, Iran.

### **Abstract**

**OBJECTIVE:** To evaluate the hypouricemic and antioxidant effects of *Allium cepa* Liliaceae (*Allium cepa* L.) and quercetin in normal and hyperuricemic rats.

**METHODS:** The following study was conducted in the Department of Nutrition and Biochemistry, Tehran University of Medical Science, Iran, between May 2007 and March 2008. A total of 48 male Wistar rats (body weights: 180-200 g) were randomly divided into 8 equal groups including normal; normal + *Allium cepa* L. (5g/kg); normal + quercetin (5mg/kg); normal + allopurinol (5mg/kg); hyperuricemic; hyperuricemic + *Allium cepa* L. (5g/kg); hyperuricemic + quercetin (5mg/kg); hyperuricemic + allopurinol (5mg/kg) once a day for 14 days. Experimentally, hyperuricemia in rats was induced by intraperitoneal injection of potassium oxonate (250mg/kg).

**RESULTS:** *Allium cepa* L. and quercetin treatments for 14 days significantly reduced ( $p=0.000$ ) the serum uric acid levels of hyperuricemic rats in a time-dependent manner. All treatments significantly inhibited hepatic xanthine oxidase/xanthine dehydrogenase activity. *Allium cepa* L. and quercetin treatments led also to a significant improvement in biomarkers of oxidative stress in hyperuricemic rats ( $p=0.000$ ). Although the hypouricemic effect of allopurinol was much higher than that of *Allium cepa* L. and quercetin, it could not significantly change oxidative stress biomarkers.

**CONCLUSION:** These results may be responsible partly for the beneficial effects of *Allium cepa* L. and its major flavonoid on hyperuricemia and oxidative stress.